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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/484,331
Filing Date: 01/18/2000
Appellant(s): HARRINGTON ET AL.

Sapna Mehtani
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed February 13, 2006 appealing from the Office action mailed 10/05/2004.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

No amendment after final has been filed.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

Bennani Declaration, submitted under 37 CFR 1.132 on April 24, 2002 (Appendix B).

Dhanoa Declaration, submitted under 37 CFR 1.132 on July 10, 2003 (Appendix C).

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 69 and 70 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The present specification provides literal support for the concept of "drug discovery", but fails to outline the method steps that would be associated with this methodology as set forth in the present claims. The gene trap vectors disclosed in the present specification and methods of use (termed RAGE technology by Appellants) are generally used to identify a sequence of interest in the genome of a cell, providing potential targets for drug discovery (specification page 32, lines 5-6). The claims are very broad in encompassing: (a) the use of any promoter in the vector system to activate any/all gene(s) in any species of cell; (b) providing and (c) screening for a non-descript "desired phenotype" implicitly associated with a particular activated gene; and (d)/(e) assaying whether a test compound can affect the phenotype of the cell or can interact with the protein encoded by the activated gene (Examiner's summary of claim 69). The method steps recited in the instant claims are not specifically associated with "drug discovery" in the instant

specification, and to provide support for the specific method steps Appellants have relied upon piecemeal support throughout the specification. Importantly, the support for the specific method steps are not associated with drug discovery, rather they are associated with methods generally associated with art recognized uses of gene trap vectors to identify affects on a cell when the expression of an endogenous gene is altered (in this case the transcription of the gene is activated). Additionally, it is noted that "determining" in step (e) is very broad encompassing any means of assay for both a "phenotype" of a cell and the ability to "interact" with a protein. The instant specification is silent with respect to any guidance or description of methodology to practice step (e).

Dependent claim 70 sets forth that the protein produced by activation of the endogenous gene is purified and exposed to a test compound. In this case, the present specification provides support for making and purifying a protein of an activated gene, however fails to provide literal or even general support for the method of "drug discovery" wherein "the test compound is exposed to the purified protein". Moreover, the specification is silent with respect to guidance and description of what the artisan would do or assess upon simply exposing a purified protein to a test compound as required in claim 70.

Methods using cells and purified proteins in identifying compounds as potential drug candidates are known and used in the art, however the cells and purified proteins used represent well characterized systems and/or targets for screening purposes. Further, generally gene trap vectors are also known in the art, and are used commonly as research tools to identify or characterize the consequence of altering gene expression in a cell. However, there is no nexus nor guidance provided in the instant specification, nor in the art of record, for providing an

artificially generated cell representing an uncharacterized system in identifying compounds as potential drug candidates.

Claims 69 and 70 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are very broad in encompassing: (a) the use of any promoter in the vector system to activate any/all gene(s) in any species of cell; (b) providing and (c) screening for a non-descript "desired phenotype" implicitly associated with a particular activated gene; and (d)/(e) assaying whether a test compound can affect the phenotype of the cell or can interact with the protein encoded by the activated gene. The specification provides working examples for the use of gene trap vectors in identifying or altering gene expression in a cell, however does not provide a single example of use of any such cell in drug discovery. The specification provides literal support for the term "drug discovery" but is silent to any guidance to practice such methods with cells or proteins. Moreover, the cells generated using the gene trap vectors (RAGE technology) represent products not normally found in nature, effectively an artificial generated system. The specification is silent with respect to any guidance in determining whether or how, generally or specifically, any cell would represent a "desired phenotype", or how this artificially activated gene expression system provides for the basis of a system of "drug discovery". It is acknowledged that the skilled artisan can practice the specific method steps required to generate cells in which a gene trap vector has been inserted the genome of a cell. Further, it is

acknowledged that the skilled artisan can practice methods of "drug discovery" using identified and characterized systems. This said, with respect to the level of skill in the art and state of the prior art (and post-filing art), there is no basis for using an artificially generated system, in this case a gene activated by gene trap vector, in drug discovery. For drug discovery, the skilled artisan requires art accepted models, or at least a well characterized system associated with something to make it a relevant system for drug discovery. In this case the use of gene trap vectors to generate cells that are not normally found in nature representing an artificial and uncharacterized system. Even if one to concede that the gene being affected is identified, as is usually done in gene trap methodology, and even conceding that it represents a sequence of a known protein associated with a specific disorder or disease, the cell generated by RAGE technology would fail to meet even the minimal requirements recognized in the art to be useful in drug discovery. By way of example, the specification provides support for known proteins of which some of them are associated with diseases (page 72, lines 22-25). The first easily recognized protein listed (second species) would be insulin as it is associated with diabetes. However, it is noted that diabetes is associated with the absence of insulin, not an over-expression as required by the claims, and so such a cell based system would not appear to be useful in drug discovery. With respect to the isolated protein, the protein itself is the "drug" used in treatment of diabetes, and would fail to serve as a target in gene discovery. Similar analogies can be made for any one of the blood clotting factors (lines 8-9) and the specific disorders associated with them. Generally, with respect to the remaining proteins listed, the artisan would recognize that the proteins themselves can have specific effects in a specific context, however are not associated with any particular disease/disorder that makes them

relevant targets of drug discovery. As noted above, often they themselves represent the compound used as a drug. For example, the first species listed erythropoietin or EPO (line 4) is used to increase red blood cell count in a patient. In the context of the claimed invention where the gene is activated and protein expression is increased., even the specific proteins listed fail to provide art accepted targets for gene discovery.

The heart of the instant rejection focuses on the nature of the invention in that the method as claimed provides for an artificially generated system for use in gene discovery. The court has stated that "patent protection is granted in return for an enabling disclosure, not for vague intimations of general ideas that may or may be workable". The court continues to say that "tossing out the mere germ of an idea does not constitute an enabling disclosure" and that "the specification, not knowledge in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement". (See *Genentech inc v. Novo Nordisk A/S* 42 USPQ2d 1001, at 1005). In this case the specification and even the art of record fails to provide a nexus between the artificially generated cell and for its use in drug discovery. Even in well characterized systems methods of identifying drug candidates can be empirical and unpredictable, and the quantity of experimentation required to practice the method as broadly claimed for all the permutations of any promoter, resulting in any resulting phenotype in any species of cell, and the enormous number of potential assays that can be used in determining an interaction would be considered undue.

(10) Response to Argument

A. Written Description Rejection under 35 USC 112, first paragraph.

Appellants summarize the basis of the rejection and provided nine points of specific argument and a summary conclusion. The issues raised in the arguments can be summarized as falling into two different groups: 1. the declarations provided during prosecution have not been properly considered (points 1, 2, 4, 5, 8 and 9); and 2. written description has been satisfied because as in this case it can be inherent, and thus not obvious (points 3, 6, 7). With respect to the declarations of Dr Dhanoa (submitted July 10, 2003) and Dr. Bennani (submitted April 29, 2003)(attached as Appendix B and C), each were formally considered and signed to this effect during prosecution. Applicants argue that the office has not considered the evidence provided in the declarations relative to the issue at hand. More specifically, it is argued that the "opinion that the person of ordinary skill in the field of drug discovery, reading this application on or about the filing date of September 26, 1997 would have realized that the Applicants, by mentioning drug discovery process as they did, implicitly were describing the drug discovery method in claims 62-69" (Appellants' brief page 3 and Dhanoa declaration page 9). Appellants note that both Dhanoa and Bennani demonstrate that the specification inherently discloses the recited steps (section 4). It is in light of this opinion and evidence, it is argued by Appellants that the office has failed to properly meet its burden for dismissing the evidence provided by the declarations. Moreover appellants argue that in light of this evidence the recited method steps are inherent and not obvious as argued by the office (Appellants brief, page 10, point 6).

Initially, it is noted that original claims 1-57 did not have methods of "drug discovery" and that new claims 58-62 drawn to this group were provided in the amendment filed January 1, 2003. Further, claims 62-68 were rejected with art under 35 USC 103 and claims 62 and 66 under 35 USC 102 (see actions mailed April 11, 2001 and October 25, 2001 respectively).

However, as noted by Appellants, claims 69 and 70 (submitted June 26, 2002) were sufficiently different from claims 62-68 that art rejections over these claims were not made.

The issue to be resolved is whether the general disclosure of "drug discovery" is sufficient to support specific method steps for practicing such a method, and whether the opinion and arguments provided in a declaration are sufficient to demonstrate that such a general disclosure provides inherent specific method steps for the method as claimed. In this case, the evidence of record fails to support Appellants arguments. For example, it is noted that the throughout prosecution, the claimed methods have been amended to address rejections of record (including art rejections) relying on the "inherent" support of the present specification. The office would acknowledge that methods of drug discovery are generally knows and practiced in the art (as summarized in the Bennani declaration pages 3-4). However, the specific and particular method steps do not bear out from such a general approach. For example, Bennani states in step (A) of drug discovery, a gene is linked to a disease state, however this is not an absolute fact of drug discovery supported by the art or record, for there are compounds tested as potential drugs where a particular gene is not indicated or a functional part of drug discovery, for example in screening cancer drugs. While a method may involve screening a wide variety of compounds, this would be done independent of implicating a gene (steps C-E, pages 3-4). Further, even if a gene were associated with a particular phenotype, a compound affecting/altering the phenotype would not uniquely involve interacting with the up-regulated gene of interest. Again by way of example, an oncogene that results in increased proliferation as in cancer, with a potential drug compound demonstrated to arrest proliferation (such as methotrexate) there would be no clear correlation between the cause and specific affect of a

phenotype/cell characteristic were being assayed. While the office would acknowledge that general methods of drug discovery are known in the art, there is no nexus for such "drug discovery" methodology and the system in which they are practiced as provided in the instant specification. The critical flaw in both declarations and the disclosure of the present specification is that the art does not recognize cells generated by the random insertion of a gene trap vector which results in the activation of an endogenous gene to be a system for drug discovery. Even when a specific gene or gene product is a target for drug discovery, an expert such as Dr. Bennani acknowledges that such a "gene is linked to a disease state by biochemical, molecular or physiological methods" (the first step in the summary of a process of drug discovery in Bennani declaration page 3). The declarations have not been found convincing because they fail to provide a nexus between the general methods of drug discovery known in the art at the time of filing and the artificial system generated by RAGE technology provided by the instant specification to support that the method steps instantly claimed are "inherent". Neither the evidence provided in the declarations Dr. Bennani and Dr. Dhanoa, nor that of the art of record supports that cells generated using gene trap vectors are a system that would be used in drug discovery, and fails to provide the necessary guidance and description of the specific method steps as now claimed.

B. Enablement Rejection under 35 USC 112, first paragraph.

Appellants discuss the procedural occurrence concerning the 35 USC 112, first paragraph, and question whether the issues of merit have been resolved. Focusing on step (e) of the method of claim 69, Appellants argue that it would be routine to practice the methods as

claimed. More generally, it is argued that providing a "desired gene and phenotype" provides the necessary point of reference for one of ordinary skill in the art to practice any specific methodology broadly known in the art and encompassed by the claim (page 17). Noting the declaration of Dr. Bannani, it is argued that "drug discovery typically utilizes an *in vitro* biochemical or cellular assay in which a gene or phenotype" of interest is activated" (page 16), and it is not necessary to create a model system of a disease to practice Appellants invention. Further, it is argued that for matters of screening details regarding the compounds being tested are not required (pages 17-18, section 3).

The office would acknowledge that in some drug screening assays compounds are practiced without knowing anything about what is being applied/tested. The outstanding issue of the 35 USC 112, first paragraph, enablement rejection is whether the instant disclosure provides the necessary guidance to practice the invention as claimed without undue burden. It is noted that the specification must teach those of skill in the art how to make and how to use the invention as broadly claimed. *In re Goodman*, 29 USPQ2d at 2013 (Fed. Cir. 1994), citing *In re Vaeck*, 20 USPQ2d at 1445 (Fed. Cir. 1991). 35 U.S.C. § 112 requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art. *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970). For enablement, the factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. Further, case law

teaches (*Ex parte Forman*, 230 USPQ 546,547 (BPAI 1986)) that "the disclosure of a patent application must enable practice of the invention claimed without undue experimentation", wherein factors involved in the determination of undue experimentation were deemed to include "the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or undpredictability of the art and the breadth of the claims."

The office would acknowledge that methods of making a cell using a gene trap vector and methods of drug discovery are generally known and practiced in the art. The issue at hand is whether the specification provides the necessary guidance to combine these two technologies/methodologies. More specifically, does a cell generated by random insertion of an activating promoter that upregulates an endogenous gene provide a tool the artisan could predictably use without undue experimentation. Discussion and arguments throughout prosecution, and as provided and dupported in the declarations of Dr. Bennani and Dr. Dhanoa, demonstrate the claims are extremely broad as to encompass the use of any cell type, any gene of interest, and the use of any assay method. The instant specification provides no literal support for the method steps as claimed with regards to a method of drug discovery, and have relied on the inherent disclosure supported by the specification for methods of drug discovery. No working examples are provided where cells generated by any gene trap vector (or more specifically by the RAGE technology noted by Appellants) are used to demonstrate the ability of such a cell to be used in drug discovery, or even in methods where a compound is applied to affect the phenotype of a cell. The state of the art, as supported by the evidence provided in the

declarations, indicate at the least a "desired" gene be associated with a disease for methods of drug discovery (Bennani declaration, page 3, step A of process). There is no art of record where gene trap vectors were used to generate materials for drug discovery, or that effectively uncharacterized cells with an interesting and a desired phenotype serve as the basis of a model system for drug discovery. There is no issue with practicing the method steps of the two different methodologies, i.e. generating cells with gene trap vectors and screening compounds in assays known in the art. The issue of enablement is that lacking a nexus between the material being tested (i.e. a cell generated using a randomly inserted gene trap vector) and the ability to reasonably interpret or associate any change of the applied compound being tested would be unpredictable and require an undue amount of experimentation. Essentially, what is required is that the artisan establish that cell or isolated protein as an appropriate target for drug discovery. It is noted that the guidance in the instant specification provides support for known proteins of which some of them are associated with diseases (page 72, lines 22-25). The first easily recognized protein listed (second species) would be insulin as it is associated with diabetes. However, it is noted that diabetes is associated with the absence of insulin, not an over-expression as required by the claims, and so such a cell based system would not appear to be useful in drug discovery. With respect to the isolated protein, the protein itself is the "drug" used in treatment of diabetes, and would fail to serve as a target in gene discovery. Similar analogies can be made for any one of the blood clotting factors (lines 8-9) and the specific disorders associated with them. Generally, with respect to the remaining proteins listed, the artisan would recognize that the proteins themselves can have specific effects in a specific context, however are not associated with any particular disease/disorder that makes them

relevant targets of drug discovery. In the context of the claimed invention where the gene is activated and protein expression is increased., even the specific proteins listed fail to provide art accepted targets for gene discovery.

The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. It is noted again that the court has stated that "patent protection is granted in return for an enabling disclosure, not for vague intimations of general ideas that may or may be workable", and that "the specification, not knowledge in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement". (See *Genentech inc v. Novo Nordisk A/S* 42 USPQ2d 1001, at 1005). In this case, the novel aspect of the invention would be the use of gene trap vectors to generate materials for drug discovery. Such an invention requires an undue amount of empirical experimentation without an reasonable expectation of success to establish the material as appropriate for use in methods of drug discovery.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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